IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ebrahim ZANDI, *et al.*
Title:	Composition and Method for Reconstituting Ikb Kinase in Yeast and Methods of Using Same
Appl. No.:	10/079,949
Filing Date:	2/19/2002
Examiner:	Prouty, Rebecca E.
Art Unit:	1652
Confirmation Number:	6542

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February 2, 2010
(Date of Transmission)

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the Pre-Appeal Brief Conference Pilot Program, announced July 11, 2005, Applicants request review of the Final Rejection dated September 2, 2009. A first reply to the Final Rejection was filed December 1, 2009. A Request and Notice of Appeal were originally due December 2, 2009. Enclosed with this Request, a Notice of Appeal and required Notice of Appeal fee, is a Petition for a Two Month Extension of Time and payment of the fee. In view of the filing of this Petition and payment of fee, a Request and Notice of Appeal are now due February 2, 2010. Accordingly, this Request is timely filed. No amendments are being filed with this Request.

REMARKS

Claims 2, 5-7, 17-19, 21-23 and 42 were examined and stand rejected in the Final Office Action. By the response filed December 1, 2009, claims 2 and 42 were amended, entry of which was refused by the Examiner in the Advisory Action mailed December 29, 2009. Because the amendment was necessitated by the erroneous rejection of the Examiner, entry of the amendment is respectfully requested. The arguments presented in this Request, however, are based on the claims examined in the Final Office Action, without the amendment.

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

35 U.S.C. § 103(a)

Claims 2, 5-7, 17-19, 21-23 and 42 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Rothwarf *et al.* (Reference C27 of Applicants' PTO-1449) in view of Traincard *et al.* (1999) *J. Cell Science* 112:3529-3535 and Epinat *et al.* (1997) *Yeast* 16:599-612.

The rejection, however, is based upon (1) a clear factual deficiency in the Examiner's interpretation of prior art and (2) the Examiner's failure to consider Applicants' amendment and arguments presented in the response filed July 28, 2009, before the Final Office Action was mailed, as required by PTO's own rule that "[o]ffice personnel should consider all rebuttal arguments and evidence presented by applicants." MPEP 2145.

(1) The prior art does not teach that NIK or MEKK1 phosphorylates IKK in the absence of any cellular context as the Examiner alleged

The Examiner alleged that because Rothwarf *et al.* discloses that NIK and MEKK1 phosphorylates IKK "*in vitro* (i.e., in the absence of any cellular context)", it is obvious that NIK and MEKK1 can phosphorylate IKK in yeast. Office Action mailed

September 2, 2009, lines 1 to 4 (emphasis added). According to the online Merriam-Webster dictionary, the term "in vitro" means "outside the living body and in an artificial environment" http://www.merriam-webster.com/, last accessed January 20, 2010. The term "in vitro", as commonly understood by the skilled artisan, does not imply a lack of cellular context, and is actually most commonly used to refer to a biological reaction being carried out in isolated cells or cell lines. The misinterpretation of this term formed an important basis for the rejection.

Subsequently, in the Advisory Action mailed December 29, 2009, the Examiner acknowledged that the term "in vitro" does not necessarily mean "in the absence of any cellular context." The Examiner, however, insisted incorrectly that, in the specific instance, the *in vitro* experiment was carried out in the absence of any cellular context.

A. NIK did not phosphorylate IKK in the absence of any cellular context

As the Examiner noted, Rothwarf *et al.* cites Ling *et al.*, (1998) *Proc. Natl. Acad. Sci. USA* **95**:3792-9 to support the statement that NIK phosphorylated IKK *in vitro*. Ling *et al.* however, discloses that both NIK and IKK proteins were first expressed in 293 cells, a human cell line, and then isolated from the cells before they were incubated together for the kinase assay. *See*, *e.g.*, page 3793, 1st column, first full paragraph and FIG. 1 legend, and page 3794, FIG. 3 legend. Ling *et al.* further teaches that NIK becomes activated before phosphorylating IKK. *Id.* page 3797, first full paragraph. Therefore, Ling et al. suggests that NIK would not be able to phosphorylate IKK without NIK first being activated in the human cells by components of the TNF-α and NF-κB signaling pathways. Because activation of NIK in the human cells is a prerequisite for NIK to phosphorylate IKK, the biochemical process of NIK phosphorylating IKK, taken as a whole, does not occur in the absence of any cellular context, or more specifically in the absence of components of the TNF-α and NF-κB signaling pathways.

Accordingly, because NIK can not be activated in yeast due to yeast's lack of the TNF-α and NF-κB signaling pathways, Ling *et al.* or Rothwarf *et al.* does not suggest that NIK can activate IKK in yeast.

B. MEKK1 did not phosphorylate IKK in the absence of any cellular context

The Examiner further noted that Rothwarf *et al.* cites Nakano *et al.*, (1998) *Proc. Natl. Acad. Sci. USA* **95**:3537-42 to support the statement that MEKK1 phosphorylated IKK *in vitro*. Nakano *et al.*, in turn, cites Lee *et al.*, (1997) *Cell* 88:213-22 to support the statement that MEKK1 phosphorylated IKK *in vitro*. *See* page 3541, 2nd column, last paragraph. Lee *et al.* however, discloses that the *in vitro* phosphorylation of IκBα kinase, an IKK protein, by MEKK1 was observed in cytoplasmic extracts of HeLa cells, a human cell line, and thus was in the presence of cellular context. *See*, *e.g.*, page 216, 2nd column, first full paragraph.

Applicants note that the molecular mechanisms by which MEKK1 is activated and MEKK1 activates IKK were not well understood at the time the application was filed. It was suspected that MEKK1 does not directly activate IKK (Karin et al. (1998) *Proc. Natl. Acad. Sci. USA* 95:9067-9, at page 9067, second column, second to the last sentence, and Figure 1). Therefore, the teachings of Rothwarf *et al.*, Nakano *et al.* or Lee *et al.* relating to IKK's phosphosphoration by MEKK1 in human cell extracts do not suggest that MEKK1 can phosphorylate IKK in yeast which lacks components, such as those of the TNF-α and NF-κB signaling pathways, critical for MEKK1's activation or phosphorylation of IKK.

Because the prior art references cited by the Office do not teach that IKK can be phosphorylated without the presence of components of the TNF-α and the NF-κB signaling pathways from human cells or cell extracts, they do not render obvious that IKK can be phosphorylated in yeast which lacks the TNF-α and the NF-κB signaling pathways.

(2) The Examiner failed to consider amendment and arguments

In the response filed July 28, 2009, claim 42 was amended to recite that the IKK protein complex is autophosphorylated and activated. Response filed July 28, 2009, page 3. Arguments supporting that the invention, as recited in the amended claim 42, is nonobvious, despite the Examiner's misinterpretation of the prior art, were also presented. *Id.* at section 4 on page 12 of the response. The Examiner, though not raising objection to the amendment, failed to consider (or, at least, comment on) the amendment or the arguments, as required by MEPE 2145.

CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that the section 103(a) rejection is based upon (1) a clear factual deficiency in the Examiner's interpretation of prior art and (2) the Examiner's failure to consider Applicants' amendment and arguments. Favorable reconsideration of the application is respectfully requested.

Respectfully submitted,

Date: February 2, 2010

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